REMARKS

Amendments to the Specification and claims

The specification has been amended at page 4, to correct a typographical error in US Publication No. 2003/0049698 of Wang et al; and at pages 17-18 to include the Accession Nos. of the hybridomas that were deposited with the ATCC. No new matter has been added by these amendments.

Elected claims 14-37 were pending in this application prior to the present amendment. Claims 14, 25, 26 and 37 are herein amended and new claims 81-89 are added.

Claim 14 is amended in sub-parts (b) and (d) to conform the indefinite articles to the following noun, and further in part (d) to clarify the term "C-terminal epitope of the gastrin hormone." These amendments do not affect the scope of claim 14.

Claim 23 is amended to depend from claim 15.

Claims 25 and 26 are amended to correct a clerical error in the ATCC accession number of the recited hybridoma; and claim 27 is amended to delete a dependence on a non-elected claim. These amendments do not affect the scope of claims 25-27.

New claim 81 is added to conform claim 81 to claims 18, 22, 26, 30 and 34.

New claims 82-89 are added to claim previously unclaimed subject matter reciting methods for determining the amount of gastrin hormone in a biological fluid sample that employ further combinations of gastrin hormone-specific antibodies.

No new matter has been added by these amendments.

Groupings of claims

Applicants offer the following table as a guide to the antibody specificity and gastrin hormone specificity recited in each of the claims:

CLAIM(S)	N-TERMINAL SPECIFICITY	C- TERMINAL SPECIFICITY	GASTRIN HORMONE SPECIFICITY
14	N-terminal epitope	C-terminal epitope	A gastrin hormone having the N-terminal epitope and the C-terminal epitope
15-18	N-terminal epitope	G17 or G34	G17 or G34
19-22	G17	G17 or G34	G17
23-26	G34	G17 or G34	G34
27-30	N-terminal epitope	G17Gly or G34Gly	G17Gly or G34Gly
31-34	G17 or G17Gly	C-terminal epitope	G17 or G17Gly
35-37 + 81	G34 or G34Gly	C-terminal epitope	G34 or G34Gly
82-85	G17 or G17Gly	G17Gly or G34Gly	G17Gly
86-89	G34 or G34Gly	G17Gly or G34Gly	G34Gly

Information Disclosure Statements

In the Office action of October 20, 2005 in the above-captioned application, the Examiner stated that the Information Disclosure Statement filed 4/18/05 (this paper was in fact filed April 15, 2005 as verified by the Certificate of Mailing), fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed.

Applicants are not aware of any defect in the copies of the cited foreign patent documents and non-patent literature publications originally submitted with the Information Disclosure Statement filed April 15, 2005.

However, as a courtesy, Applicants herewith resubmit copies of the cited foreign patent documents and non-patent literature publications originally submitted with the Information Disclosure Statement filed April 15, 2005, along with a copy of the original PTO Form 1449 as originally submitted.

The Office Action of October 20, 2005 further states that the second Information Disclosure Statement filed on 7/18/05 (this paper was in fact filed July 14, 2005 as verified by the Certificate of Mailing) fails to comply with 37 C.F.R. § 1.98(a)(1). Specifically, the Examiner states that the copy of the document by Wang et al. was not considered because it was not listed on an Information Disclosure Statement.

The Information Disclosure Statement filed July 14, 2005 does not cite the Wang et al. J. Clin. Inv. (1996) 1918-1929, Vol. 28 reference, because it is listed in the Information Disclosure Statement filed April 15, 2005, albeit with a typographical error. The listing in the Information Disclosure Statement of April 15, 2005 cites the authors as Watson et al (See line 6, page 3 of 4).

Applicants herewith resubmit the Information Disclosure Statement of April 15, 2005 and respectfully request that the courtesy copies of the references cited in therein be accepted with the original filing date of April 15, 2005.

The Invention

The claimed invention relates to a method for determining the amount of free gastrin hormone in a biological fluid sample. The gastrin hormone may be in the form of G17, G17Gly, G34 or G34Gly.

The method includes the steps of:

(a) obtaining a biological fluid sample comprising a gastrin hormone from a patient;

(b) providing an immobilized antibody that selectively binds an N-terminal epitope of the gastrin hormone;

(c) incubating the sample under suitable conditions for binding of the gastrin hormone in the sample to said antibody to produce an immobilized complex of the antibody bound to the gastrin hormone;

(d) washing the immobilized complex to remove unbound antibody, and reacting the complex with a suitable detectable marker-conjugated antibody that selectively binds a C-terminal epitope of the gastrin hormone;

(e) washing the immobilized detectable marker-conjugated antibody complex, and incubating with a development reagent; and

(f) measuring the developed reagent to determine the amount of free gastrin hormone in the biological fluid sample.

ARGUMENT

Rejections under 35 U.S.C. § 112, first paragraph

I. Claims 18, 22, 26, 230 and 34 were rejected under 35 U.S.C. § 112, first paragraph as allegedly relating to subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. According to the Office Action, the specification does not disclose a repeatable process for obtaining the monoclonal antibodies required to practice the invention and it is not apparent if the biological material or source materials are both known and readily available to the public.

In fact, the eight hybridomas that produce monoclonal antibodies disclosed in the specification were deposited with the American Type Culture Collection (ATCC, Manassas, VA), an approved depositary under the Budapest Treaty. The deposited hybridomas were:: 400-1 producing MAb 400-1; 400-2 producing MAb 400-2; 400-3 producing MAb 400-3; 400-4 producing MAb 400-4; 401-2 producing MAb 401-2; 445-1 producing MAb 445-1; 445-2 producing MAb 445-2; and 458-1 producing MAb 458-1.

Applicants attach a copy of a declaration by John M. McCafferty, an officer of Aphton Corporation that affirms that the deposits were made under the requirements of the Budapest Treaty, including a statement that the deposits will be irrevocably released to the public without restriction upon issuance of a patent from the pending application (or a copending application disclosing the same hybridomas), or a continuation, a continuation-in-part or a divisional application based on either of these applications.

Therefore, Applicants assert that the rejection of claims 18, 22, 26, 230 and 34 under 35 U.S.C. § 112, first paragraph for alleged failure to enable the invention for the alleged lack of availability of the disclosed monoclonal antibodies is misapplied and should be withdrawn.

II. Claims 14-37 were rejected under 35 U.S.C. § 112, first paragraph as allegedly relating to subject matter that was not enabled by the description in the specification. According to the Office Action, the specification while being enabling for a biological fluid from a human subject, does not reasonably provide enablement for a biological fluid from other sources.

Applicants gratefully acknowledge the Patent Office's determination that the specification is enabling for human biological fluid samples. However, Applicants respectfully point out that claim 14 and its dependent claims relate to a "method for determining the amount of free gastrin hormone in a biological fluid sample, comprising the steps of (a) obtaining a biological sample comprising a gastrin hormone from a patient..."

Clearly, pending claims 14-37 and 81-89 as recited hereinabove relate to obtaining a biological fluid from a human ("a patient"), the human biological fluid comprising human gastrin hormone.

Therefore, Applicants respectfully assert that the rejection of claims 14-37 for alleged lack of enablement is misapplied and should be withdrawn. New claims 81-89 each depend from claim 14, or from one or more claims that themselves depend from claim 14. Similarly, new claims 81-89 also recite the same limitation in step (a) and likewise cannot properly be rejected under 35 U.S.C. § 112, first paragraph for alleged failure to provide enablement of gastrin hormone detection in biological fluid samples from other sources.

Rejections under 35 U.S.C. § 112, second paragraph

I. Claims 14 and 15-16; 19-20; 23-24; 27-28; 31-32 and 35-36 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite in reciting an "N-terminal" and a "C-terminal" of gastrin hormone. According to the Examiner, these terms are unclear as to which amino acids of gastrin hormone would be considered to be within the "N-terminal" or the "C-terminal."

Applicants respectfully traverse this rejection. The present application incorporates by reference the specification of US Provisional Application No.60/577,759 (the '759 application, co-filed with the present application on March 29, 2004). One of ordinary skill on reading the disclosure of the present application would readily understand that the terms "N-terminal" epitope and the "C-terminal" epitope of gastrin hormone relate to epitopes found within the amino acid sequences of the gastrin hormone at the N-terminus and the C-terminus, respectively, of the gastrin hormone.

For example, the antibodies that bind to an epitope at the N-terminus of G17 (and also of G17Gly, since this gastrin form has an identical N-terminal amino acid sequence) bind an epitope found within the amino acids sequence pEGPWLE (SEQ ID NO:5), as incorporated by reference from the '759 application into the present specification. Similarly, the antibodies that bind to an epitope at the C-terminus of G17 (and also of G34, since this gastrin form has an identical C-terminal amino acid sequence) bind an epitope found within the amino acids sequence EEAYGWMDF(NH_2) (SEQ ID NO:6), also incorporated by reference from the '759 application. Further, the antibodies that bind to an epitope at the N-terminus of G34 bind an epitope found within the amino acids sequence pELGPQG (SEQ ID NO:7), incorporated by reference from the '759 application. Finally, the antibodies that bind to an epitope at the C-terminus of G17Gly (and also of

G34Gly, since this gastrin form has an identical C-terminal amino acid sequence) bind an epitope found within the amino acids sequence YGWMDFG (SEQ ID NO:8), as incorporated by reference from the '759 application.

Therefore, Applicants maintain that the terms an "N-terminal" and a "C-terminal" of gastrin hormone are clear and definite and that this rejection of claim 14 for alleged failure to point out and distinctly claim the subject matter of the invention should be withdrawn.

II. Claim 14 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite in reciting a "biological fluid sample comprising gastrin hormone from a patient."

Applicants maintain that the phrase "biological fluid sample comprising gastrin hormone from a patient" would be clearly understood by anyone of skill in the art as referencing a human biological fluid comprising a human gastrin hormone. Every example and every description of a biological fluid and a gastrin hormone in the specification relate to human samples and hormones.

Therefore, the recitation in claim 14 of a "biological fluid sample comprising gastrin hormone from a patient" is clear and definite. Applicants respectfully request that this rejection of claim 14 for alleged failure to point out and distinctly claim the subject matter of the invention should be withdrawn.

III. Claim 14 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the recitation of "suitable conditions" in part (c) and also for the recitation of "suitable detectable marker-conjugated antibody" in part (d). According to the Examiner, it is unclear whether the suitable antibody of the claim is one that selectively binds a C-terminal epitope, or if there are other factors that would render the antibody suitable or unsuitable.

Applicants again traverse this rejection. The binding of an antibody to an antigen, and the use of detectable marker-conjugated antibodies are well characterized and highly predictable arts. Therefore, one of ordinary skill would immediately understand which conditions and which detectable marker-conjugated antibodies are suitable for use in the claimed invention.

In fact the specification refers the reader to a published guide to the state of the art in immunoassays: At page 3, third complete paragraph, last sentence: "See for example: "*Principles and practice of Immunoassay*" (1991) Christopher P. Price and David J, Neoman (eds) Stockton Press, New York, NY."

Therefore, Applicants believe that the rejection of claim 14 as allegedly indefinite for the recitation of "suitable conditions" in part (c) and also for the recitation of "suitable detectable marker-conjugated antibody" in part (d) is inaposite and must be withdrawn.

III. Claim 14 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the recitation of an antibody that "selectively binds a[n] C-terminal epitope bound to the gastrin hormone" in part (d). According to the Examiner it Is not clear whether the epitope is a C-terminal epitope of the gastrin hormone or a C-terminal epitope of some other mioety bound to the gastrin hormone.

Part (d) of claim 14 has been amended to recite "selectively binds a C-terminal epitope of the gastrin hormone." Therefore, Applicants maintain that part (d) of claim 14 as amended is clear and definite, and respectfully request that this rejection be withdrawn.

IV. Claims 21, 25, 29, 33 and 37 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the recitation of a monoclonal antibody that "has the characteristics of" a

recited monoclonal antibody. According to the Office Action, it is unclear what characteristics are referred to.

Applicants respond that one of skill in the art would readily determine those characteristics from the specification and from the well known principles of immunoassays that was common knowledge among practitioners of skill in the art. For instance, several characteristics of monoclonal antibodies are discussed at page 3, second paragraph of the specification: These include:

"...characteristics: 1) the fine specificity for the molecular composition and tertiary structure of the epitope; 2) the antibody idiotype; 3) the antibody affinity; 4) the antibody allotype; 5) the antibody isotype."

Therefore, Applicants maintain that claims 21, 25, 29, 33 and 37 are clear and definite, and respectfully request that this rejection be withdrawn.

V. Claims 21and 26 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the recitation of hybridoma 400-2 and 401-2, respectively, as these hybridomas were stated to have the same ATCC accession number (PTA-5890).

Applicants have amended claim 26, and also claim 25, which had incorrectly assigned ATCC accession numbers. These claims now correctly recite hybridoma 401-2 as having ATCC accession number PTA-5893.

Therefore the rejection of claims 21and 26 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness must now be withdrawn.

Rejections under 35 U.S.C. § 103(a)

I. In the Office Action of October 20, 2005, claims 14-17, 19-21, 27-29 and 31-33 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Goetze et al. (Clin. Chem. 49: 333-334, Feb. 2003), (Herein after referred to as "Goetze et al.") in view of Yokoi et al. US Patent 5,643,735 ("Yokoi et al."), and Berg et al. (Biochemistry, W.H. Freeman and Co. 2002, sections 4.3.1-4.3.3 and Fig. 4.35), (Hereinafter "Berg et al.").

Applicants point out that there are least four species of gastrin hormone as described in the present specification at page 1, last complete paragraph:

> ...gastrin exists in several forms, grouped into two major size classes, "little" gastrin and "big" gastrin, on the basis of the number of amino acid residues in the peptide chain. The "little" gastrin form includes mature gastrin-17 (G17) and glycine-extended G17 (G17-Gly); and "big" gastrin includes gastrin-34 (G34) and glycine-extended G34 (G34-Gly)...
>
> ...Human G34 has the entire seventeen amino acid sequence of G17 at its C-terminal, and, predictably, cross-reacts immunologically with G17.

As summarized above, the present invention provides an assay method capable of distinguishing these gastrin hormone forms (G17, G34, G17Gly and G34Gly). The Goetze et al. reference does not disclose any such capability. Goetze et al. describe an assay that measures the sum of G17 and G34 species, since the assay is based on detection with an antibody that is directed to a C-terminal epitope common to both G17 and G34. Moreover, nowhere in Goetze et al. is there any description of an assay method that is capable of distinguishing and measuring a single gastrin hormone species. In fact, Goetze et al. state "Gastrin assays for diagnostic purposes (usually RIA or ELISA) should preferably measure all forms of gastrin." Goetze, page 333, col. 1, para. 2, lines 3-5.

Therefore, Goetze et al., far from leading those of skill in the art to the present invention, actually teaches away from the presently claimed methods, because Goetze et al. favor assays that measure the combined amounts of all gastrin forms. By contrast, the present invention provides methods for distinguishing and separately measuring the gastrin hormone forms

Yokoi et al. relates to immunological assay for Thymosin α1. Nowhere in Yokoi et al. is there any reference to gastrin hormone. Moreover, the method disclosed in Yokoi et al. is designed to measure the level of the single species of Thymosin α1 and does not distinguish different forms of Thymosin α1 hormone, much less different forms of gastrin hormone.

Berg et al. is a general reference to immunoassays, including those based on monoclonal antibodies. Nowhere in Berg et al. is there any disclosure or even a hint of separately measuring the amounts of different gastrin hormone forms.

In fact, there would be no reason for one of skill in the art to combine the disclosures of Goetz et al. and Yokoi et al., as there is neither any invitation, nor any suggestion to combine these disclosures within their texts, since they relate to different hormone species (one, gastrin with multiple hormone forms, and the other, Thymosin α1 with only one recognized form). As discussed above, even if the combination were permitted (which it is not), Berg et al. fails to add anything to the disclosure of Goetze et al. that would lead one of skill in the art to an assay for measuring each of the different gastrin hormone forms (G17, G34, G17Gly and G34Gly).

Therefore, Applicants assert that claims 14-17, 19-21, 27-29 and 31-33 are not obvious over Goetze et al. in view of Yokoi et al., and Berg et al. For this reason Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 103(a) be withdrawn.

II. In the Office Action, claims 22 and 34 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied above, and further in view of Grimes et al. (US Patent Application Publication No. 2002/0058040, hereinafter "the '040 application"). According to the Examiner, Goetze et al. discloses every aspect of the methods of claims 22 and 34 except for the monoclonal antibodies produced by the hybridomas 400-1, 400-2, 400-3 and 400-4. Further, the Examiner cites the '040 application at paragraphs 25 and 104-125 as disclosing anti-hG17 monoclonal antibodies 400-1, 400-2, 400-3 and 400-4 in a method for determining G17 gastrin hormone.

Applicants point out that the '040 application discloses an RIA using a mixture of the anti-hG17 monoclonal antibodies 400-1, 400-2, 400-3 and 400-4 in a method for determining G17 gastrin hormone. Nowhere in the '040 application is there any disclosure of a sandwich immunoassay as recited in claims 22 and 34. Furthermore, nowhere in any of the cited references is there any suggestion of the use of any of the monoclonal antibodies 400-1, 400-2, 400-3 or 400-4 in combination with a gastrin hormone C-terminal selective monoclonal antibody in a sandwich immunoassay for the determination o f the amount of a single gastrin hormone form.

Therefore, Applicants maintain, claims 22 and 34 cannot be held to be obvious over the disclosure of Goetze et al. in view of Yokoi et al., and Berg et al. further in view of the '040 application. For this reason, the rejection of claims 22 and 34 under 5 U.S.C. § 103(a) as allegedly unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied above, and further in view of Grimes et al. cannot stand and must be withdrawn.

III. In the Office Action, claims 23-25 and 35-37 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied above, and further in view of Gevas et al., US Patent No. 5,607,676 (hereinafter, "the '676 patent"). According to the Examiner, the combination of Goetze et al. in view of Yokoi et al. and Berg et al. as applied above, as applied to claims 14-17, 19-21, 27-29 and 31-33, discloses every aspect of the methods of claims 23-25 and 35-37 except for the monoclonal antibodies selective for the N-terminus of G34 or Gly-extended G34. Further, the Examiner cites the '676 patent (at Col. 6, lines 1-47; Example 1, "peptide 5 in particular; and Col. 11, lines 60-65; Col. 12, Table 2, "Immunogen 5" in particular and lines 50-59) as disclosing G34-specific antibodies that specifically target amino acid residues at the amino terminus of G34.

Applicants again maintain that the combination of the disclosures of Goetze et al. in view of Yokoi et al. and Berg et al. as applied by the Examiner fail to disclose an immunoassay method for separately measuring the amounts of different gastrin hormone forms as claimed in claims 23-25 and 35-37. The '676 patent discloses antibodies to the N-terminus of G34 or Gly-extended G34; and also an immunoassay using these antibodies.

The immunoassay disclosed in the '676 patent that uses the antibodies to the N-terminus of G34 or Gly-extended G34 is a radioimmunoassay (RIA). Radioimmunoassays are distinct from the sandwich immunoassay methods of the invention of claims 23-25 and 35-37. There is no disclosure, nor even any suggestion to use the antibodies to the N-terminus of G34 or Gly-extended G34 in a sandwich immunoassay method for separately measuring the amounts of different gastrin hormone forms.

Nowhere in the combination of cited references is there any invitation or suggestion to use a C-terminal specific antibody in addition to the antibodies to the N-terminus of G34 or Gly-extended G34 of the '676 patent to provide a sandwich immunoassay method for separately measuring the amounts of different G34 and G34Gly gastrin hormone forms as claimed in claims 23-25 and 35-37 of the present application.

Absent such an invitation or suggestion to use both N-terminal-specific and C-terminal-specific anti-gastrin antibodies, there can be no finding of obviousness of a sandwich immunoassay based on the use of these two terminal-specific antibodies as recited in claims 23-25 and 35-37. Therefore, Applicants assert that the rejection of claims 23-25 and 35-37 under under 35 U.S.C. § 103(a) as allegedly unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied above, and further in view of Gevas et al., US Patent No. 5,607,676, is misapplied and should be withdrawn.

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This Response is being filed with a Petition for a Two Month Extension of Time.

Applicants respectfully request reconsideration of the objections and rejections raised in the Office Action of October 20, 2005.

Should any additional fee be deemed necessary in connection with this filing or to maintain pendency of the application, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 23-1703.

Dated: February 28, 2006

Respectfully submitted,

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